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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,841	01/19/2000	Roy A. Gravel	50004/003004	3640

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,841	GRAVEL ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-9,11-21,35-39 and 42-54* is/are pending in the application.

4a) Of the above claim(s) *12,15-20 and 45-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9, 11, 13, 14, 21, 35-39, 42-44 and 50-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 4-22-04 has been entered. Claims 6, 35 and 42 have been amended. Claims 40 and 41 have been canceled. Claims 43-54 have been added. Claims 6-9, 11-21, 35-39 and 42-54 are pending.

It should be noted that claims 45-49 are directed to a method for detecting an increased risk of a folate/cobalamin metabolic disorder in a mammal by detecting the presence of a homozygous MTRR polymorphism. The subject matter of claims 45-49 is patentably distinct from that of previously examined claims 6-9, 11, 13, 14, 21 and 35-43 which are directed to a method for detecting an increased risk of developing a neural tube defect, Down's Syndrome or cardiovascular disease in a mammalian embryo or fetus or a method for detecting an increased risk of Down's syndrome, hyperhomocysteinemia, cardiovascular disease or cancer in a mammal. Thus, claims 45-49 will not be considered by examiner in the instant Official action.

Claims 6-9, 11, 13, 14, 21, 35-39, 42-44 and 50-54 are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 6 recites the limitation "said neural tube defect" in line 8. There is insufficient antecedent basis for this limitation in the claim. The phrase "a neural tube defect" in claim 6 has been deleted in the amended claim 6. Claims 7-9, 11, 13, 14, 21, 36 and 38 depend on claim 6 but fail to clarify the indefiniteness. Applicants' amendment filed 4-22-04 necessitates this new ground of rejection.

3. Claim 11 recites the limitation "developing a neural tube defect" in line 6. There is insufficient antecedent basis for this limitation in the claim. Applicants' amendment filed 4-22-04 necessitates this new ground of rejection.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 6-9, 11, 13, 14, 21, 35-39, 42 and 43 remain rejected and claims 44 and 50-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased risk for mothers to develop neural tube defects (NTD) with combination of homozygous mutant MTRR genotype having an A/G polymorphism at base 66, which yields an isoleucine (22I) or a methionine (22M) at amino acid position 22, and low cobalamin; increased risk to develop NTD when case mother or case child has both homozygous MTRR 66 A/G mutation and homozygous methylenetetrahydrofolate reductase (MTHFR) 677 C/T mutation (SEQ ID No. 51); mothers of Down's Syndrome babies are more likely to have homozygous MTRR polymorphism of A->G at nucleotide position 66 and MTHFR polymorphism C->T at nucleotide position 677 than control mothers; and individuals having a MTRR homozygous 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 59, 63, 66, 68), does not reasonably provide enablement for a method for detecting an increased risk of developing a NTD, Down's Syndrome, hyperhomocysteinmia, cancer or cardiovascular disease in a mammal or any

mammalian fetus or embryo by detecting any heterozygous or homozygous MTRR polymorphism in either or both future parents of said embryo or fetus, or in said embryo or fetus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 11-20-03. Applicant's arguments filed 4-22-04 have been fully considered but they are not persuasive.

Claims 44 and 50-54 are newly added. Claim 44 depends from claim 6 or 35 and specifies the cancer is colon cancer. Claims 50-54 are directed to a method for detecting an increased risk of developing a neural tube defect in a mammalian embryo or fetus comprising detecting the presence of a homozygous A66G MTRR polymorphysm in an embryo or fetus or a future parent of said embryo or fetus, or a homozygous or heterozygous A66G MTRR polymorphysm in both future parents of said embryo or fetus, in combination with low serum cobalamin.

Applicants cite page 63, line 4, to page 64, line 1 of the specification and argue that the presence of an MTRR A66G mutation in an embryo or fetus or a future parent of the embryo or fetus is sufficient to indicate the increased risk of having a Down's Syndrome baby (amendment, p. 12-14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-20-03. The claims encompass detecting an increased risk of developing Down's Syndrome in a mammalian embryo or fetus by detecting homozygous MTRR polymorphysm in an embryo or fetus, or a future parent of said embryo or fetus, or by detecting either a homozygous or heterozygous MTRR polymorphysm in both future parents, wherein said polymorphysm comprises an A66G mutation. The specification only discloses that mothers of

Down's syndrome babies are more likely to have **homozygous** MTRR polymorphism of A->G at nucleotide position 66 than control mothers. The specification fails to provide adequate guidance and evidence for the correlation between the homozygous MTRR A66G mutation of a father or heterozygous MTRR polymorphysm of both future parents and the increased risk of developing Down's syndrome in a mammalian embryo or fetus. As discussed in the Official action mailed 11-20-03, different polymorphism or mutation within a gene could result in dramatic different effect on the function of the gene product and NTD, Down's Syndrome, hyperhomocysteinemia, cancer and cardiovascular disease are different diseases that differ pathologically and differ in their mechanisms in developing those diseases. Therefore, different MTRR polymorphism or mutation would have different correlations with increased risk of developing a NTD, Down's Syndrome, hyperhomocysteinemia, cancer, or cardiovascular disease. It was unpredictable at the time of the invention whether a mutation or polymorphism of MTRR or in combination with other gene mutation, or other factor, would increase the risk of developing NTD, Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal or a fetus or an embryo. There is no evidence of record that the homozygous MTRR A66G mutation of a father or heterozygous MTRR polymorphysm of both future parents is correlated to the increased risk of developing Down's syndrome in a mammalian embryo or fetus.

Applicants cite specification page 32, line 22, to page 33, line 4 and page 8, lines 14-20, and argue that the method of detecting mutation of MTRR and the presence of the mutation or polymorphysm is an indication that the animal has an increased or decreased likelihood of developing hypercysteinemia, cardiovascular disease, neural tube defect, or cancer. Applicants

further cite specification page 45, lines 10-13 and argue that cell line WG1401 shows A66G polymorphysm and WG1401 is from patient with megaloblastic anemia, hyperhomocysteinemia, and mild methylmalonic aciduria (amendment, p. 14-15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-20-03 and the reasons set forth above. It was unpredictable at the time of the invention whether a mutation or polymorphism of MTRR or in combination with other gene mutation, or other factor, would increase the risk of developing NTD, Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal or a fetus or an embryo. The specification only provides a general statement that "the presence of the mutation or polymorphysm is an indication that the animal has **an increased or decreased likelihood** of developing hypercysteinemia, cardiovascular disease, neural tube defect, or cancer". The specification fails to provide adequate guidance and evidence for what mutation or polymorphysm of MTRR contributes to an increased or **decreased** likelihood of developing cancer. There is no evidence of record that any homozygous or heterozygous MTRR polymorphism, such as A66G mutation, in an embryo or fetus, or any future parent of said embryo or fetus, has any correlation with increased risk of developing any cancer, including prostate cancer, breast cancer, any brain cancer, colon cancer, hepatoma, melanoma, leukemia etc., in a mammal or in an embryo or fetus. Further, the presence of A66G polymorphysm in cell line WG1401 does not mean that A66G polymorphysm is correlated to any type of cancer. It appears that further study is required to confirm the correlation between the MTRR polymorphisms and **increased** risk of developing the cancer, such as colon cancer, in a mammal or in an embryo or fetus. The method of identifying the MTRR polymorphisms is only a tool of identification but it is not necessary that the MTRR polymorphisms are correlated to increased

risk of developing the cancer, such as colon cancer. The specification must provide sufficient enabling disclosure for the claimed invention but fails to do so.

Applicants cite Matsuo reference that suggests the A66G MTRR polymorphysm is a risk factor for colorectal cancer. Applicants also cite Stolzenberg-Solomon reference and argue that there is a correlation between the presence of the A66G MTRR polymorphsym and esophageal squamous cell carcinoma (amendment, p. 15-16). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-20-03 and the reasons set forth above. The effective filing date of the present invention is 1-16-98, which is 4 or 5 years before the publication date of Matsuo reference and Stolzenberg-Solomon reference. The specification only provides a general statement that "the presence of the mutation or polymorphysm is an indication that the animal has **an increased or decreased likelihood** of developing hypercysteinemia, cardiovascular disease, neural tube defect, or cancer". The specification fails to point out what polymorphysm of MTRR is correlated to an increased risk of developing a cancer. Further, there are numerous different types of cancer and the specification fails to provide adequate guidance and evidence for whether the A66G MTRR polymorphysm is correlated to all types of cancer. The specification fails to provide sufficient enabling disclosure for the claimed invention and one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. Thus, claims 6-9, 11, 13, 14, 21, 35-39, 42 and 43 remain rejected and claims 44 and 50-54 are rejected under 35 U.S.C. 112 first paragraph.

Applicants argue that the specification is enabling for new claims 50-54 (amendment, p. 18). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-20-03 and the reasons set forth above.

Conclusion

No claim is allowed.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.